Role of endothelial surface layer in regulating the sodium balance and extracellular fluid volume

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON40170

Source
ToetsingOnline

Brief title
SALT study

Condition

- Other condition
- Vascular hypertensive disorders

Synonym
blood pressure, extracellular volume, sodium and volume homeostasis, sodium buffering capacity of ECL

Health condition

fysiologie van natrium- en volumebalans

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMW en de Nederlandse Nierstichting

Intervention

Keyword: blood pressure, endothelial surface layer, extracellular volume, natrium

Outcome measures

Primary outcome

We will study primarily the effects of a salt load on the haemodynamics and ECV in subjects with a presumed normal ESL in healthy subjects.

Primary endpoint will be the ECV as represented by body weight and BP.

Furthermore, the golden standard for ECV measurement will be performed.

Secondary outcome

Other study paramaters consist of indirect measurements of the ESL dynamics and function as assessed with intravital microscopy of the sublingual microvasculature and transcapillary escape rate (TER). We will study the kidney function as represented by the glomerular filtration rate (GFR), fractional Na+ excretion, albuminuria and proteinuria. Finally, skin biopsies will allow study of the role of interstitial GAGs and macrophage influx in response to a salt load.

Study description

Background summary

Sodium (Na+) plays a key role in maintaining volume homeostasis and blood

pressure (BP). The difference between Na+ intake and excretion, the Na+ balance, is regulated by the kidney. Regulation of the Na+ balance by the kidney is believed to be the main determinant of extracellular fluid volume (ECV). Recent studies have revealed that the Na+ balance is not only regulated by the kidney, but also in the interstitium of the skin. Here, binding of Na+ to glycosaminoglycans (GAGs) allows non-osmotic handling of Na+, thereby acting as a Na+ buffer. Based on these findings, we hypothesize that the endothelial surface layer (ESL), representing a complex sugar layer principally composed of negative-charged GAGs lining the endothelium, is an important determinant of volume homeostasis and BP by its ability to act as an immediate non-osmotic Na+ buffer. Furthermore, a perturbed ESL might lead to an increased ECV and BP response after a salt load. The volume of the ESL varies highly between individuals (0.5-2.3 L) and is know to be smaller in specific patient groups like diabetes type 1 and patients with chronic kidney disease. Due to its function in vascular physiology, including mechanotransduction, hemostasis, and blood cell-vessel wall interactions, the ESL is instrumental for vascular permeability, which might also be influenced by the Na+ buffering capacity of ESL.
The putative non-osmotic buffer capacity of the endothelial GAGs without commensurate water retention has only been limitedly studied yet, but seems particularly relevant in clinical conditions characterized by volume overload (e.g., heart failure, hypertension, chronic kidney disease). If the endothelial GAGs are involved in non-osmotic Na+ storage, treatment strategies directed to restoration of the ESL would lead to improved BP and ECV control and, conceivably, to better cardiovascular outcome. This study focuses on a novel function of the ESL, namely the capacity to store Na+ non-osmotically.

Study objective

In this study we will identify the role of the endothelial GAGs in Na+ and volume homeostasis. Is there a link between the ESL and an individual its susceptibility to Na+-excess?

In a following study the Na+ buffering capacity of the intact ESL will be compared to diabetes mellitus type 1 patients (acquired perturbed ESL) and Hereditary multiple exostosis patients (defective heparan sulphates polymerization).

Study design

In this project, we plan to conduct an experimental interventional cross-over study to investigate the Na+ storing capacity of the endothelial GAGs. For this, different Na+ conditions and the effect on ESL, ECV and BP, will be studied in healthy subjects.

Intervention

All subjects will be asked to adhere to a low and high natrium diet (3 and 12 grams salt daily respectively, which is equal to 50 mmol Na+/d and 200 mmol Na+/d respectively) for 1 week each in random order.
Furthermore, all subjects will receive a hypertonic salt infusion at day 8 of the low salt diet to study the effects of an acute salt load. The subjects will also receive a LPS infusion on day 8 of the high salt diet as modulator of ESL.

Study burden and risks

The burden of this study consists of 4 visits for healthy subjects. They will spend about 21 hours in the research departmenet. All subjects will be asked to adhere to a low and a high Na+ diet. The study comprises extra venous blood drawing and various extra diagnostic tests. Invasive measurements with different tracers for ECV and GFR (ioxehol), plasma volume (PV) and TER (125I-albumin) will take place. The radiation exposure is *minor* (maximum 0,1 mSV). Also, subjects will receive a low dose of LPS-endotoxin for modulating the ESL. LPS infusion might cause transient characteristic clinical symptoms like chills, headache, myalgia and nausea.
At present, the function of the ESL in relation to salt intake and CVD is not well understood. Novel strategies for targets for treatment of complex diseases with concepts of volume overload are prevalent. For our healthy study subjects there is no direct benefit when participating in this study, but the outcome of the study is essential for further investigations on this topic. The findings of this study might influence future treatment for diseases characterized by an expanded ECV (e.g. dietary salt restriction or diuretics).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy subjects
- Male between 18 and 40 years of age
- Healthy, as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination (PE) and laboratory tests carried out in the screening visit.
- Non-treated office blood pressure * 140/90 mmHg
- Capable of giving written informed consent and able to comply with the requirements and restrictions listed in the informed consent form

Exclusion criteria

- An office blood pressure >140/90 mmHg
- A body mass index > 30 kg/m2
- A major illness in the past 3 months or any significant chronic medical illness that the Investigator would deem unfavourable for enrolment, including chronic inflammatory diseases
- A history of any type of malignancy within the past 5 years with the exception of successfully treated basal cell cancer of the skin
- A history of any renal disease
- A history of cardiovascular disease (in the past 6 months) defined as documented coronary artery disease including myocardial infarction, (un-)stable angina pectoris or acute coronary syndrome, precutenaous transluminal coronary angioplasty, coronary artery bypass grafting, cerebrovascular disease including ischemic and hemorrhagic stroke or a subarachnodial bleeding, or peripheral artery disease including aortic aneurysmata
- A history of coagulation disorders
- A history of primary hyperlipoproteinemias
- A history of hypersensitivity or allergy to iodium or to shell fish

- A history, within 3 years, of drug abuse (including benzodiazepines, opioids, amphetamine, cocaine, THC, methamphetamine)
- A history of alcoholism and/or is drinking more than 3 units of alcohol per day. Alcoholism is defined as an average weekly intake of >21 units for males. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits
- Difficulty in donating blood or limited accessibility of a vein in left and right arm
- Subject has donated blood in last 3 months
- Use of tobacco products
- Any other issue that, in the opinion of the Investigator, could be harmful to the subject or compromise interpretation of the data
- Prior participation in a trial where the subject received intravenous endotoxin (LPS) infusion
- Any clinically relevant abnormality noted on the 12-lead ECG as judged by the Investigator or an average QTcB or QTcF > 450 millisec

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-09-2013
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO

Date:	23-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	27-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 24712
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL42890.018.13
OMON	NL-OMON24712